UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA	)	
	)	
v.	)	CR. NO.: 05-40033-FDS
	)	
THOMAS VIGLIATURA	)	

GOVERNMENT'S SUBMISSION IN SUPPORT OF ITS MOTION FOR DETENTION

In support of its Motion for Detention the government submits two recent articles from the New England Journal of Medicine concerning the dangers of GHB, once of the drugs the defendants conspired to distribute.

Respectfully submitted,

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By:

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Close Calls with Club Drugs

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Around midnight one night in 1999, I was radioed by the EMTs: they were bringing in two ``drunk'' college students. This was hardly an uncommon occurrence. Many a college student has been mortified to wake up in the emergency room looking into the eyes of a college administrator who knew that a stressful semester or a campus party could spell danger. Widespread alcohol abuse on college campuses and its sometimes fatal consequences have long raised alarm, and the signs and symptoms of cocaine or marijuana abuse are commonly known.

But there was something different about these students. Apparently healthy college men, they had been drinking at a party when the girlfriend of one noticed that they had disappeared. Worried, she went looking for them. She found them unconscious in the basement of the building, and she couldn't wake them. She might have left them there to sleep it off, but she called for help instead.

The EMTs who responded thought that the students were simply drunk, but the students' level of consciousness decreased alarmingly en route to the hospital. By the time they arrived, both young men were deeply comatose -- unresponsive to all stimuli, including pain. As the EMTs were filling me in, I noticed that one of the patients had stopped breathing. Within a few minutes, both of them had to be intubated.

Had these men been left in the basement, they would have been brain-dead within about six minutes after they had stopped breathing, and their hearts would have stopped shortly thereafter. As it was, both required mechanical ventilation for the rest of the night.

What had these students taken? They didn't smell of alcohol. There were no track marks on their arms. There was no evidence of trauma or other disease. In fact, what was so alarming was how healthy they looked -- they had simply stopped breathing.

None of their friends in the waiting room could tell me what drugs were involved, although there were murmurings of ``G,'' ``liquid E,'' and ``vitamins'' -- street names for (gamma)-hydroxybutyric acid (GHB), 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy), and methamphetamine. Blood and urine drug screens were negative except for alcohol, but the level of ethanol was not high enough to cause

respiratory arrest. These patients were not alcoholics, not IV drug abusers. They were student athletes nearing graduation from college with the whole world ahead of them.

As an emergency physician, I had watched the evolution -- and treated the clinical consequences -- of the abuse of legal and illegal drugs from the hallucinogens of the 1960s to the stimulants and opiates of the 1970s and the cocaine of the 1980s. Now I was encountering the difficulties of diagnosing abuse of the so-called club drugs -- which, unfortunately, many people still erroneously believe to be harmless.

The most commonly used club drugs are GHB, MDMA, flunitrazepam, and ketamine. Instructions for making them with the use of chemicals found in household products, over-the-counter medications, and prescription drugs can be found on Internet sites, rendering them accessible and inexpensive. They are also potentially deadly.

In this case, I believe that the culprit was GHB (discussed by Snead and Gibson in this issue of the Journal, pages 2721-2732). Clear, odorless, tasteless, and thought to be an aphrodisiac and an amnesic, GHB unfortunately makes a perfect date-rape drug. But the euphoria that begins 20 to 30 minutes after ingestion can quickly evolve into more toxic effects, including dizziness, nausea and vomiting, myoclonic jerks, confusion, agitation, hallucination, and seizure. In combination with alcohol, GHB can cause decreased respiratory drive, coma, and death. There is currently no metabolite that can be measured on routine toxicology screens, so although some laboratories can now test for GHB, the results are not available on an emergency basis.

I don't know whether these students are aware of how close they came to dying. Because they arrived at the hospital when they did, they were able to walk out the following day, remembering little or nothing of the entire event. Given their friends' comments, their profound respiratory depression, the duration of the effects, and the subsequent amnesia, my guess is that they combined GHB with alcohol. But the amnesia made it impossible to get an accurate history.

Clearly, alcohol, tobacco, and marijuana are not the only temptations out there for our children. Club drugs can be taken in pill or liquid form -- no snorting, smoking, or needles required. Given the deceptively innocuous qualities of these drugs, it is important to raise awareness of their potentially devastating effects.

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Drug Therapy: (gamma)-Hydroxybutyric Acid

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The short-chain fatty acid (gamma)-hydroxybutyric acid (GHB) was synthesized in 1960 in an attempt to create an analogue of the ubiquitous inhibitory brain neurotransmitter (gamma)-aminobutyric acid (GABA) that would cross the blood-brain barrier. (Ref. 1) GHB turned out to have sedative properties similar to those that had been reported for (gamma)-butyrolactone 13 years earlier. (Ref. 2) In fact, (gamma)-butyrolactone has since been shown to be biologically inactive, (Ref. 3,4) since all its biologic and behavioral effects are due to its rapid conversion to GHB by an active lactonase. (Ref. 5) Although GHB has found limited clinical use as an anesthetic agent (Ref. 6-8) and in the treatment of narcolepsy (Ref. 9) and alcoholism, (Ref. 10) widespread interest has developed during the past 5 to 10 years because GHB has emerged as a major recreational drug and public health problem in the United States. GHB has diverse neuropharmacologic and neurobiologic properties and appears to have dual neuronal mechanisms of action that include activation of both the (gamma)-aminobutyric acid type B (GABA(sub B)) receptor and a separate, GHB-specific receptor (Table 1). This complex interaction between GHB and the GHB and GABA(sub B) receptors within mesocorticolimbic dopamine pathways is probably responsible for the addictive nature of GHB and for symptoms of withdrawal from it.!*Table 1.-Molecular Mechanisms and Physiological Consequences of Ingestion of GHB (Ref. 11-13,16,17,19-21,23-26,28-30) *.**TABLE OMITTED**

Neuropharmacologic Features

Metabolism and Neuromodulatory Properties

GHB occurs naturally in mammalian brain tissue, (Ref. 31) where it is derived from the conversion of its parent neurotransmitter, GABA, (Ref. 32) to succinic semialdehyde through mitochondrial GABA transaminase (Figure 1). Succinic semialdehyde is then reduced to GHB by cytosolic succinic semialdehyde reductase. (Ref. 14) GHB may be metabolized through the action of GHB dehydrogenase to succinic semialdehyde, which may be further metabolized either to GABA by GABA transaminase or to succinate through the action of mitochondrial succinic

semialdehyde dehydrogenase. (Ref. 33)!*Figure 1.-Putative Metabolic Interrelationship of GHB with (gamma)-Butyrolactone and 1,4-Butanediol.The most important synthetic pathway for (gamma)-hydroxybutyric acid (GHB) entails conversion of (gamma)-aminobutyric acid (GABA) to succinic semialdehyde by mitochondrial GABA transaminase, followed by reduction of succinic semialdehyde to GHB by cytosolic succinic semialdehyde reductase. Mitochondrial succinic semialdehyde dehydrogenase, converting succinic semialdehyde to succinate, couples neurotransmitter metabolism to mitochondrial energy production. This is the enzyme missing in clinical and experimental deficiency of succinic semialdehyde dehydrogenase. A minor pathway for GHB production involves partial oxidation of 1,4-butanediol. Systemically administered (gamma)-butyrolactone is converted by a circulating lactonase to GHB. This lactonase is not present in brain tissue. The most significant catabolic pathway for GHB degradation is the oxidation of GHB to succinic semialdehyde by NADP(sup +)-linked succinic semialdehyde reductase. The resultant succinic semialdehyde undergoes further metabolism to either GABA or succinate. A mitochondrial NADP(sup +)-independent transhydrogenase is capable of metabolizing GHB to succinic semialdehyde with the production of D-2-hydroxyglutaric acid from L-2-hydroxyglutarate and an end product of 4,5-dihydroxyhexanoate. There is disagreement as to whether there is significant metabolism of GHB through a (beta)-oxidation scheme *.**FIGURE OMITTED**

GHB exerts ubiquitous pharmacologic and physiological effects when it is administered systemically to animals (Table 1). (Ref. 34) However, GHB also has many of the requisite properties of a neurotransmitter or neuromodulator, (Ref. 35) including a discrete, subcellular anatomical distribution in neuronal presynaptic terminals, along with its synthesizing enzyme. GHB is released by neuronal depolarization in a calcium-dependent fashion. (Ref. 36) A sodium-dependent GHB-uptake system in the brain has also been described, (Ref. 37) and an active vesicular uptake system that is most likely driven by a vesicular inhibitory amino acid transporter has been reported. (Ref. 38)

GHB Receptors

The existence of a specific GHB receptor is suggested by specific, high-affinity GHB-binding sites that are observed in the brains of rats and humans. The kinetics of the GHB receptor are related to the 1-to-4-microm concentration of GHB that is typically found in mammalian brain tissue. (Ref. 14,31) Although there are contradictory data, (Ref. 39) evidence suggests that the GHB receptor is presynaptic and G-protein-coupled (Ref. 15) and that it may function to inhibit the release of GABA. (Ref. 18) Despite data showing that GHB may be biologically active in its own right, compelling evidence suggests that most of the physiologic and pharmacologic effects of systemically administered GHB are mediated by the GABA(sub B) receptor (Table 1).

GABA Receptors

GABA is ubiquitous in the brain and can activate ligand-gated ion channels -- GABA type A (GABA(sub A)) and GABA type C (GABA(sub C)) receptors -- as well as GABA(sub B) receptors. Activation of the GABA(sub A) receptor results in the influx of chloride ions and the generation of a fast inhibitory postsynaptic potential (Figure 2). (Ref. 41) There is little evidence to support the hypothesis that GHB interacts with the ionotropic GABA(sub A) receptor. (Ref. 42)!*Figure 2.-Synthesis and Release of GHB and GABA at Synapses.The diagram shows the presynaptic and

postsynaptic effects of endogenously released (gamma)-hydroxybutyric acid (GHB) (as indicated by dashed arrows) and (gamma)-aminobutyric acid (GABA) (as indicated by solid arrows) and the effects of the exogenously administered GHB, as in abuse and addiction. GABA is synthesized from glutamate in inhibitory neurons and in turn gives rise to GHB. Both GHB and GABA are released on depolarization of the GABA-releasing (GABAergic) neuron. GABA, in forms that are either endogenous or derived from exogenously administered GHB, acts on GABA(sub A) and GABA(sub B) receptors (GABA(sub A)R and GABA(sub B)R, respectively). GABA(sub A) receptors are ionotropic and, when activated by GABA, cause fast postsynaptic inhibition by the efflux of chloride ions (Cl(sup -)). GABA(sub B) receptors are metabotropic and, when activated by either GABA or high concentrations of GHB, induce slow postsynaptic inhibition by activating potassium (K(sup +)) currents. Presynaptic GABA(sub B) autoreceptors -- when activated by GHB, GABA, or both -- reduce the release of GABA by suppressing the influx of calcium (Ca(sup 2+)). Both endogenous and exogenous forms of GHB have a dual action on the GHB receptor (GHBR) and the GABA(sub B) receptor. GHB that binds with high affinity to the presynaptic GHB receptor decreases the release of GABA; GHB that binds to a low-affinity site on the GABA(sub B) receptor increases activation of cell-surface receptors by inhibiting constitutive and agonist-induced endocytosis. The result is enhancement of GHB function mediated by GABA(sub B) receptors, with a greater effect on presynaptic inhibition than on postsynaptic inhibition. Adapted from Owens and Kreigstein (Ref. 40) *.**FIGURE OMITTED**

The GABA(sub B) receptor mediates a slow inhibitory postsynaptic potential. Effector mechanisms associated with the GABA(sub B) receptor include signaling through the action of the adenylate cyclase system and activation of calcium channels and G-protein-coupled, inwardly rectifying potassium channels. The GABA(sub B) receptor is a heterodimer composed of receptor 1 and receptor 2 subunits. The GABA(sub B) receptor is transported from the interior of the cell to the cell surface by the receptor 2 subunit. Postsynaptic GABA(sub B) receptors are coupled to G-protein-coupled, inwardly rectifying potassium channels. Presynaptic GABA(sub B) receptors are subdivided into those that control the release of GABA (autoreceptors) and those that inhibit the release of all other neurotransmitters (heteroreceptors). GABA(sub B) receptors mediate their presynaptic effects through voltage-dependent inhibition of high-voltage-activated calcium channels (Figure 2). (Ref. 43)

GHB and GABA(sub B) Receptors

Because of the structural similarity of GHB to GABA and the pharmacologic GABA(sub B)-like effects of GHB, the question of whether the GHB receptor and the GABA(sub B) receptor are the same has been raised, and data have been conflicting on this point. However, the results of recent studies, taken in conjunction with older data, suggest that the GHB receptor and the GABA(sub B) receptor are separate and distinct. (Ref. 22,44,45)

GHB binds to the GHB receptor and the GABA(sub B) receptor with high affinity and low affinity, respectively. Available biochemical data (Ref. 14,15) suggest that the intrinsic neurobiologic activity of GHB is mediated through the GHB receptor. However, many of the pharmacologic, clinical, behavioral, and toxicologic effects of exogenously administered GHB (Table 1) appear to be mediated through the GABA(sub B) receptor, where GHB may act both directly, as a partial GABA(sub B) receptor agonist, (Ref. 45,46) and indirectly, on the GABA(sub B) receptor, through

GHB-derived GABA. (Ref. 47) The micromolar concentrations of GHB that are normally present in mammalian brain tissue (Ref. 31) can activate GHB receptors but are insufficient to activate GABA(sub B) receptors, for which GHB has a weak affinity. However, the supraphysiologic (i.e., millimolar) concentrations of GHB that result from systemic administration (Ref. 4) of this compound have been shown to compete for binding sites at the GABA(sub B) receptor, (Ref. 35,48) activate recombinant GABA(sub B) receptor heterodimers, (Ref. 45,49) and have an electrophysiological effect that is blocked by a specific GABA(sub B) receptor antagonist but not by a GHB antagonist. (Ref. 46,50)

In addition to being a weak partial agonist of the GABA(sub B) receptor, GHB may also activate the GABA(sub B) receptor indirectly, through its conversion to GABA (Figure 2). This hypothesis could explain the inordinately high concentration of GHB required to produce GABA(sub B)-receptor-mediated effects, since high micromolar to low millimolar concentrations of GHB are required to produce enough GHB-derived GABA to activate GABA(sub B) receptors. (Ref. 47) Furthermore, recent data suggest that GHB-derived GABA activates the GABA(sub B) receptor and induces endocytosis of the GABA(sub B) receptor, whereas GHB itself opposes this process and, acting at the GABA(sub B) receptor, causes the GABA(sub B) receptor to be retained on the cell surface, thus prolonging the functionality of the receptor. (Ref. 51)

Thus, experimental evidence to date suggests that the high concentrations of GHB in brain tissue that would be predicted to accrue from exogenous administration of this compound (Ref. 4) -- as occurs in the clinical scenarios of GHB intoxication, addiction, and abuse -- may exert their protean pharmacologic, toxicologic, and behavioral effects primarily through mechanisms mediated by the GABA(sub B) receptor (Figure 2).

Toxicity, Abuse, Addiction, and Withdrawal

GHB Toxicity

GHB has a half-life of 20 to 30 minutes, plasma levels peak about 40 minutes after oral ingestion, and the compound can be detected in urine for up to 12 hours. (Ref. 52) GHB has a narrow margin of safety. Doses of 20 to 30 mg per kilogram of body weight lead to euphoria and memory loss, as well as to drowsiness and sleep. However, coma may result when twice this dose (or more) is administered. (Ref. 53) In some series, GHB was the second most common drug detected in the serum of young people presenting with drug-induced coma, just behind cocaine. (Ref. 54)

The clinical hallmark of GHB overdose is rapid onset of profound coma, myoclonus, respiratory depression, hypoventilation, and bradycardia. These signs persist for an unusually short time, given the depth of the coma. (Ref. 53) The usual rapid and uneventful recovery from GHB intoxication can create a false sense of security in the GHB user. (Ref. 55) The level of consciousness in patients with GHB-induced coma does not correlate with the serum level of GHB. (Ref. 56) GHB intoxication should be considered in any patient, particularly any young man, who presents with rapid onset of coma of unknown cause when head trauma, metabolic disorders, central nervous system infection, and increased intracranial pressure have been ruled out.

Death from an overdose of GHB may occur as a result of respiratory compromise, aspiration, positional asphyxia, or pulmonary edema, (Ref. 53,57,58) as well as

traumatic injury or accident, possibly due to the abrupt loss of consciousness induced by GHB. (Ref. 53,59) Well over half of all patients who present with GHB intoxication have abused other drugs as well. (Ref. 60,61) Chief among these drugs is ethanol, which is synergistic with GHB in the induction of respiratory depression and hypotension (Ref. 62) and thus increases the risk of an adverse outcome with an overdose of GHB.

The management of GHB intoxication in a patient who is spontaneously breathing is primarily supportive and includes stabilization of the airway, establishment of intravenous access, oxygen supplementation, and administration of atropine for persistent bradycardia. (Ref. 53,63,64) Intubation is rarely indicated but should be performed in the presence of marked hypoventilation, hypoxemia, or mucosal ulcerations or in the absence of the gag response. (Ref. 53) Mucosal ulcerations are of concern because illicit forms of GHB are often made from (gamma)-butyrolactone and sodium hydroxide, an extremely basic mixture that causes mucosal burns. Aspiration of this mixture into the lungs can lead to serious pulmonary complications. (Ref. 57)

There are no specific antidotes to GHB, nor is there a role for naloxone or flumazenil in the reversal of GHB-induced coma. (Ref. 65) Activated charcoal is not indicated because of the very short half-life of GHB and the risk of aspiration. (Ref. 53) Although physostigmine has been used to reverse the clinical signs of GHB intoxication, there is insufficient evidence to recommend its use in the treatment of GHB toxicity. (Ref. 66) A patient who has recovered within six hours after the onset of symptoms can be discharged, because GHB has a relatively short half-life, and patients usually have a rapid and uneventful recovery from an overdose of GHB. Before discharge, the cause of the GHB toxicity should be determined -- in other words, did the overdose occur accidentally during a one-time recreational use, or did it occur in the context of repeated GHB abuse? Discharge plans should be made accordingly, to provide the patient with assistance in dealing with the issues that led to the GHB overdose. This strategy is particularly important in the avoidance of GHB withdrawal if chronic GHB abuse led to the overdose. Any patient with a recovery time that is longer than six hours should be admitted to the hospital.

GHB Abuse

Since the early 1990s, GHB and its prodrugs, (gamma)-butyrolactone and 1,4-butanediol, have been used and abused by bodybuilders (Ref. 67) because these compounds were reported to stimulate the production of growth hormone (Table 2). (Ref. 27) Like (gamma)-butyrolactone, 1,4-butanediol has behavioral and toxic effects caused primarily by its metabolism to GHB by an alcohol dehydrogenase. (Ref. 72,73) However, the diol itself carries inherent toxicity and is particularly dangerous when used in conjunction with ethanol, which enhances its toxicity, probably because of competition of the two compounds for alcohol dehydrogenase. (Ref. 74)!*Table 2.-Clinical Aspects of GHB Overdose, Abuse, Addiction, and Withdrawal *.**TABLE OMITTED**

By the late 1990s, GHB had become a popular club drug and had gained substantial notoriety both as a major recreational drug of abuse (Ref. 55,62,68) and as a ``date rape'' drug. (Ref. 75) Subsequently, data on the addictive properties of these compounds began to emerge. (Ref. 59) In 1990, the Food and Drug Administration had banned the sale of nonprescription GHB; in 2000, the agency classified it as a Schedule I substance. (Ref. 76) However, illicit forms of GHB

remain available under a number of names, such as G, liquid ecstasy, grievous bodily harm, Georgia home boy, liquid X, soap, easy lay, salty water, scoop, cherry meth, and nitro. (Ref. 53,69) In addition, (gamma)-butyrolactone and 1,4-butanediol are still available for purchase on the Internet, where they are advertised for mood enhancement, sleep induction, and bodybuilding. (Ref. 77)

The abuse of GHB and its congeners, (gamma)-butyrolactone and 1,4-butanediol, probably stems from the euphoria, disinhibition, and heightened sexual awareness said to be experienced after administration of the drug. (Ref. 69) The psychic effects of GHB have been likened to those of ethanol in combination with reduced anxiety, feelings of euphoria, enhanced sensuality, and emotional warmth. (Ref. 53) The resultant dreamy, altered sensorium accompanying the use of GHB has made it popular among attendees of so-called circuit parties (Ref. 77) or ``raves''. (Ref. 60) Raves, all-night dance parties attended by large numbers of young people, are characterized by clandestine venues, hypnotic electronic music, and the liberal use of drugs, among them GHB. (Ref. 78) Circuit parties differ from raves in that they are usually attended by men who are either bisexual or homosexual. (Ref. 77) When used at raves and circuit parties, GHB frequently is ingested along with other illicit drugs, most commonly ethanol, methylenedioxymethamphetamine (MDMA, or ``ecstasy''), or cocaine. (Ref. 60) The abuse of GHB at raves and other party settings appears to be far more prevalent among men than among women. (Ref. 61,69,79)

GHB poses a serious risk for persons who are infected with the human immunodeficiency virus who are taking protease inhibitors, since these compounds alter the metabolism of GHB through their interaction with the cytochrome P-450 system. The result is that even small doses of GHB in the presence of these compounds may lead to the classic signs of GHB overdose (i.e., coma and respiratory compromise). (Ref. 80,81)

GHB Addiction

GHB is highly addictive. (Ref. 76) Occasional users of the drug may be at risk for rape, overdose, or death, given the settings in which occasional use occurs, but occasional users are unlikely to become addicted. Frequent users who take GHB as an antidepressant or for sleep, weight loss, or the enhancement of bodybuilding are far more likely to become addicted. (Ref. 59) Some GHB users describe rebound insomnia or alertness occurring after two or three hours of sleep, an effect that often leads them to take additional doses to return to sleep. Thus, such users may ultimately escalate the dosage to one dose every two to four hours, around the clock. (Ref. 82) GHB users typically do not see GHB as a drug because of assurances they find in publications and on the Internet that it is a ``safe'' and ``natural'' product. (Ref. 83) Therefore, the GHB user may ignore warnings from friends and family who may comment about increasingly bizarre behavior; users also generally fail to recognize their incipient addiction until withdrawal ensues. (Ref. 84)

Protocols for the treatment of GHB addiction and systematic detoxification have not been published, to our knowledge. However, it would make sense to consider the use of baclofen, a GABA(sub B) receptor agonist, for such therapy, since this compound appears to be effective in reducing the need for addictive drugs in animal models of GHB addiction as well as cocaine, heroin, and ethanol addiction. (Ref. 85,86)

GHB Withdrawal

Frequent ingestion of GHB can be associated with severe, potentially life-threatening withdrawal symptoms, necessitating vigorous clinical management, preferably in an inpatient setting. (Ref. 62,69,82) Although occasional users of GHB may have a mild withdrawal syndrome when the drug is discontinued, those who have been taking GHB every one to three hours can have severe symptoms similar to those of withdrawal from ethanol or benzodiazepine. (Ref. 70) In dependent persons, withdrawal symptoms may start within one to six hours after cessation of the drug. (Ref. 69) Although most withdrawal symptoms occur in those who have taken the drug every one to three hours, such symptoms have also been noted in persons who have used the drug every eight hours. In contrast, cessation of GHB prescribed in the context of once-daily dosing for narcolepsy usually does not lead to withdrawal symptoms. (Ref. 70)

The minimum daily dose of GHB that is associated with withdrawal is reported to be 18 g; for (gamma)-butyrolactone, it is 10 g. (Ref. 54) However, the major caveat concerning these data is the lack of quality and quantity controls with respect to the ingestion of GHB. Since most patients who present with GHB toxicity or withdrawal have purchased the drug illegally, the purity and size of the described ``capful'' or ``teaspoon'' doses are quite variable, ranging from 500 mg to 5 g per dose. (Ref. 59) As in other forms of addiction and abuse, most patients who present in GHB withdrawal are male. (Ref. 69) Most of them have been taking GHB for less than two years, and about 75 percent have been using GHB, rather than precursors such as (gamma)-butyrolactone. (Ref. 54)

GHB withdrawal symptoms may be mild on presentation, but they may increase in intensity and severity over hours or days and culminate in delirium or frank psychosis. The most common features of withdrawal are tremor, tachycardia, restlessness, insomnia, anxiety, nausea, and vomiting. Delirium, often with diaphoresis and hypertension, occurs in people with severe dependence. (Ref. 59,69) Death from GHB withdrawal caused by pulmonary edema has been reported. (Ref. 69)

Symptoms of withdrawal from GHB may last up to two weeks. In addition to the acute GHB withdrawal syndrome, a prolonged withdrawal state lasting from three to six months and characterized by dysphoria, anxiety, memory problems, and insomnia has been reported. (Ref. 87) A person with protracted or untreated symptoms of GHB withdrawal may abuse either alcohol or benzodiazepines in an attempt to relieve anxiety and insomnia.

The mainstay of therapy for GHB withdrawal is supportive care and sedation to prevent injury, hyperthermia, and rhabdomyolysis. Physical restraint may be required in about one third of patients. (Ref. 69) Benzodiazepines (either lorazepam or diazepam), often in very high doses, are the primary agents used to treat GHB withdrawal (Ref. 53,69-71,82) because they have a broad therapeutic range, a high threshold for respiratory depression, and are relatively free of cardiovascular complications. Antipsychotic agents are not indicated in the management of GHB withdrawal and have the added disadvantage of lowering the seizure threshold. (Ref. 70) However, there is no evidence that anticonvulsant drugs are effective in the treatment of GHB withdrawal. (Ref. 70) In withdrawal that is refractory to benzodiazepines, pentobarbital administered in the intensive care setting is said to be effective. (Ref. 69-71,88) Multiple relapses after GHB detoxification in patients who have gone through addiction and withdrawal are common, as are insomnia, depression, and abuse of other drugs. (Ref. 84)

GHB-Facilitated Sexual Assault

GHB has received substantial notoriety during the past several years as a date-rape drug -- in other words, a compound used to facilitate sexual assault. Low doses of GHB (10 to 20 mg per kilogram) induce short-term antegrade amnesia, increased libido, euphoria, suggestibility, and passivity, all of which contribute to the use of GHB in sexual assaults. (Ref. 75,89-91) Populations that are at high risk for drug-facilitated sexual assault include single women or men in unfamiliar social settings. The sodium salt of GHB is generally available as a liquid that is colorless, odorless, and water-soluble and tastes slightly salty; this liquid can be easily and surreptitiously added to a drink without detection by the intended victim. Drug administration may occur in a bar or club, when the recipient is inattentive or accepts a drink or an already opened bottle. (Ref. 92)

Most of the published evidence of GHB in this role is anecdotal; ethanol and benzodiazepines appear to be more commonly used in drug-facilitated assault. (Ref. 93,94) However, GHB should be considered in cases of sexual assault that occur after drinking and a social encounter, particularly when the patient has a gap in memory. In making a diagnosis of GHB-facilitated sexual assault, it is important to collect samples of blood and urine as soon as possible after the alleged assault and to measure GHB levels with the proper analytic techniques. Since GHB is undetectable by the usual toxicologic screens, laboratory diagnosis of GHB-facilitated assault is challenging. GHB levels may be determined in plasma and urine samples by gas chromatography-mass spectrometry with selected-ion monitoring. (Ref. 95) Although this analytic technique for the detection of GHB is not readily available, it may be performed by state and national reference laboratories. (Ref. 56)

Putative Mechanisms of Action

The dopamine neurons in the brain are involved in reward-dependent learning; therefore, neurons involved in abuse, addiction, and withdrawal have their cell bodies in the ventral tegmental area and project into the basal forebrain structures, such as the nucleus accumbens, amygdala, and frontal and limbic cortexes (Figure 3). (Ref. 96,99,100) Activation of these mesocorticolimbic dopaminergic neurons, with a resultant increase in the output of dopamine in innervated projection structures, has been reported with virtually all major drugs of abuse. Conversely, during abstinence there is a marked decrease in the activity of dopaminergic neurons in the ventral tegmental area. (Ref. 99) Therefore, the mesocorticolimbic circuitry of the brain is a likely target for GHB in abuse, addiction, and withdrawal.!*Figure 3.-Mesocorticolimbic Dopaminergic Pathways Putatively Involved in the Mechanism of GHB.These pathways have been defined in the rat brain (Ref. 96); a similar map for the human brain does not exist and can only be extrapolated. The dopaminergic neurons in this circuit have their cell bodies in the ventral tegmental area, from which they project to the nucleus accumbens, amygdala (not shown), and prefrontal cortex. Under normal circumstances, the dopaminergic neurons in this circuitry are under inhibitory control by both noradrenergic fibers from the locus ceruleus and GABAergic neurons in the ventral tegmental area. However, in the presence of GHB, which is unable to stimulate postsynaptic GABA(sub B) receptors in the ventral tegmental area, (Ref. 97) there is a preferential action at GABA(sub B) autoreceptors, with decreased release of GABA and resultant disinhibition of dopaminergic neurons in the circuit. This

disinhibition is further accentuated by GHB-mediated inhibition of noradrenergic neurons from the locus ceruleus. (Ref. 98) The result is increased activity of dopaminergic mesocorticolimbic circuitry in the presence of increased levels of GHB in the brain; addiction then develops. Minus signs denote inhibition, and plus signs disinhibition. Adapted from Gardner and Lowinson (Ref. 96) *.**FIGURE OMITTED**

Although a variety of neurotransmitters interact with mesocorticolimbic dopamine pathways, (Ref. 99) the mechanism of action that would explain the addictive properties of GHB appears to be related to the effects of dopamine mediated by GABA(sub B) receptors (Ref. 101) in mesocorticolimbic circuitry. However, the reported finding that GHB decreases dopaminergic neuronal activity in the ventral tegmental area and thereby reduces the release of dopamine into the nucleus accumbens (Ref. 102) poses a conundrum, since drugs of abuse are classically associated with an increase in the neuronal activity of mesocorticolimbic dopamine.

A potential explanation for this paradox may lie in recently published experiments (Ref. 97) showing that GHB is unable to activate potassium channels mediated by GABA(sub B) receptors in dopamine neurons in the ventral tegmental area. However, GHB was able to activate GABA(sub B) receptor-mediated potassium channels in GABA-releasing (GABAergic) neurons of the ventral tegmental area because of a difference in the expression of potassium-channel subunits between the dopaminergic and GABAergic neurons. GHB also is known to decrease the release of GABA by a presynaptic, GHB-specific action. (Ref. 15,18) Hence, in GHB abuse and addiction, which are accompanied by an increased concentration of GHB in the brain, GHB may inhibit GABAergic neurons preferentially and decrease the release of GABA through effects mediated by GABA(sub B) receptors and GHB receptors, respectively. The result would be a disinhibition of dopaminergic neurons of the ventral tegmental area with increased dopaminergic activity within that circuitry (Figure 3), which in turn would lead to the psychic symptoms that accompany GHB abuse and addiction. This hypothesis would also explain the difference between GHB, which is addictive, and the GABA(sub B) receptor agonist baclofen, which is not. In fact, baclofen may be useful in decreasing the reinforcement effects of cocaine, heroin, nicotine, ethanol, (Ref. 85) and GHB, (Ref. 86) probably by reducing the release of dopamine in the ventral tegmental area. Finally, GHB has been recently shown to decrease the activity of neurons in the locus ceruleus, (Ref. 98) providing yet another route by which GHB could disinhibit mesocorticolimbic dopaminergic circuitry (Figure 3).

In summary, data indicate that the mechanism of GHB abuse, addiction, and withdrawal may be due to inhibition of GABAergic neurons by mechanisms mediated by GABA(sub B) receptors and inhibition of presynaptic GABA release in mesocorticolimbic dopaminergic pathways by a mechanism mediated by GHB receptors, with a resultant disinhibition of dopamine neurons and increase in dopaminergic activity in the mesocorticolimbic circuitry (Figure 3).

Future Directions

The pharmacologic properties of GHB and its GABA(sub B) receptor-mediated effects are well known. However, the neurobiologic function of GHB remains elusive. This function will probably be delineated after the successful molecular cloning of the primary GHB receptor in brain tissue and the subsequent engineering of mice with mutant GHB receptors. These developments will lead to a more precise elucidation of the relationship between the GHB receptor and GABA(sub B) receptor and will

facilitate careful investigation of the relative contributions of GHB-induced GABA synthesis, GHB-induced alterations in GABA release, and the signaling pathways involved in GHB-induced alteration of intracellular movement of GABA(sub B) receptors. In a similar fashion, a mutant mouse that is deficient in succinic semialdehyde dehydrogenase (Ref. 103) may provide insight into the mechanisms of GHB addiction and withdrawal because it has inordinately high levels of GHB and GABA in brain tissue. Given the experimental evidence of the efficacy of the GABA(sub B) receptor baclofen in GHB abuse, (Ref. 85,86) controlled, prospective clinical trials of this compound in the treatment of GHB addiction and withdrawal and of a GABA(sub B) receptor antagonist (Ref. 104) in the treatment of GHB overdose will be important.

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---- INDEX REFERENCES ----

NEWS SUBJECT: (Stress Related Illnesses (1ST30); Social Issues (1SO05); Alcohol Abuse (1AL63); Health & Family (1HE30); Drug Addiction (1DR84); Crime (1CR87); Sex Crimes (1SE01))

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